MND–SMART
Clinical trials for MND

A platform for flexible, efficient, & definitive Phase 3 MND trials

NHS Lothian R&D Conference 2025

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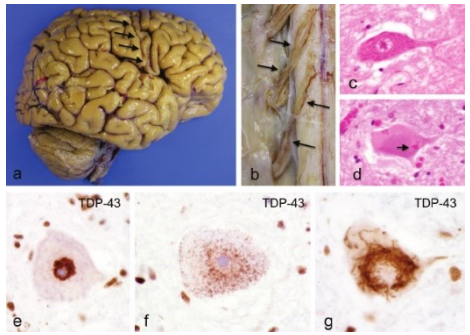
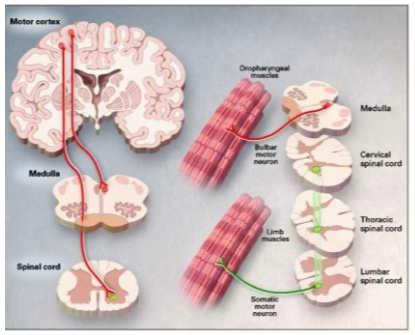
MND–SMART
Clinical trials for MND





Motor neuron disease

- Limb weakness, speech/swallowing, breathing difficulties
- 50% cognitive/behaviour change, 15% dementia
- Time to reach diagnosis: 1 year
- Average survival: 2-3 years, 30% die within 1 year
- Lifetime risk 1:300

- Affects motor cortex, spinal tracts, anterior horn cells
- TDP-43 pathology in 97%

- Only 1 licensed drug globally – poor efficacy

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Clinical trials for MND

Only 1 licensed therapy in the UK: riluzole - approved by FDA in 1995 - prolongs life by 2-3 months

Due to a lack of definitive benefit for most drugs tested recently, only tofersen (SOD 1 associated MND) has received approval in Europe

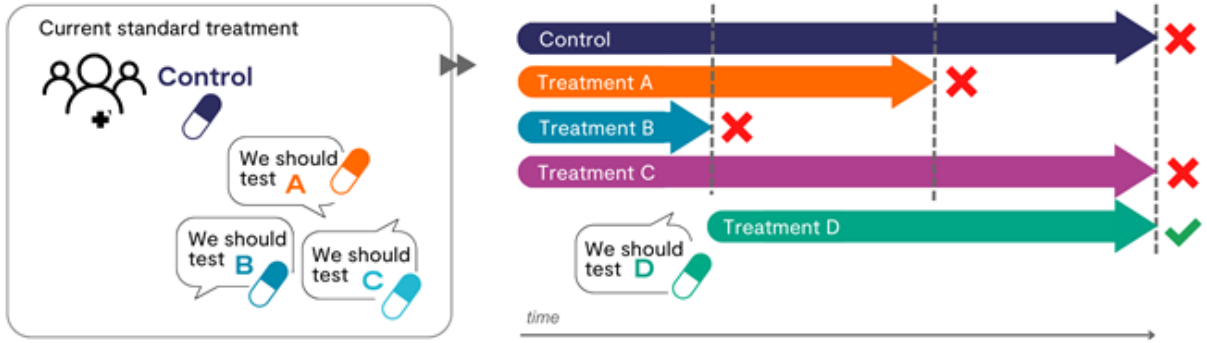
< 10% of people with MND participated in trials before 2020

Urgent need for: 1) Effective new treatments, 2) Increased participation, 3) Innovation in clinical trial design.

Multi-Arm Multi-Stage (MAMS) adaptive Platform Trials

STAMPEDE | MSSMART | ROSSINI 2 | MND–SMART Clinical trials for MND | RECOVERY | Octopus Advancing clinical trials for progressive MS | EJS ACT PD Accelerating Clinical Trials in Parkinson's The Edmond J Safra ACT PD initiative | AD SMART

2005 2013 2018 2020 2023 2025



Faster
Multiple treatments tested at the same time

Facilitates recruitment
Fewer patients required overall

Cost
No need to set up a new trial for each treatment

Flexibility
Drop and add treatments

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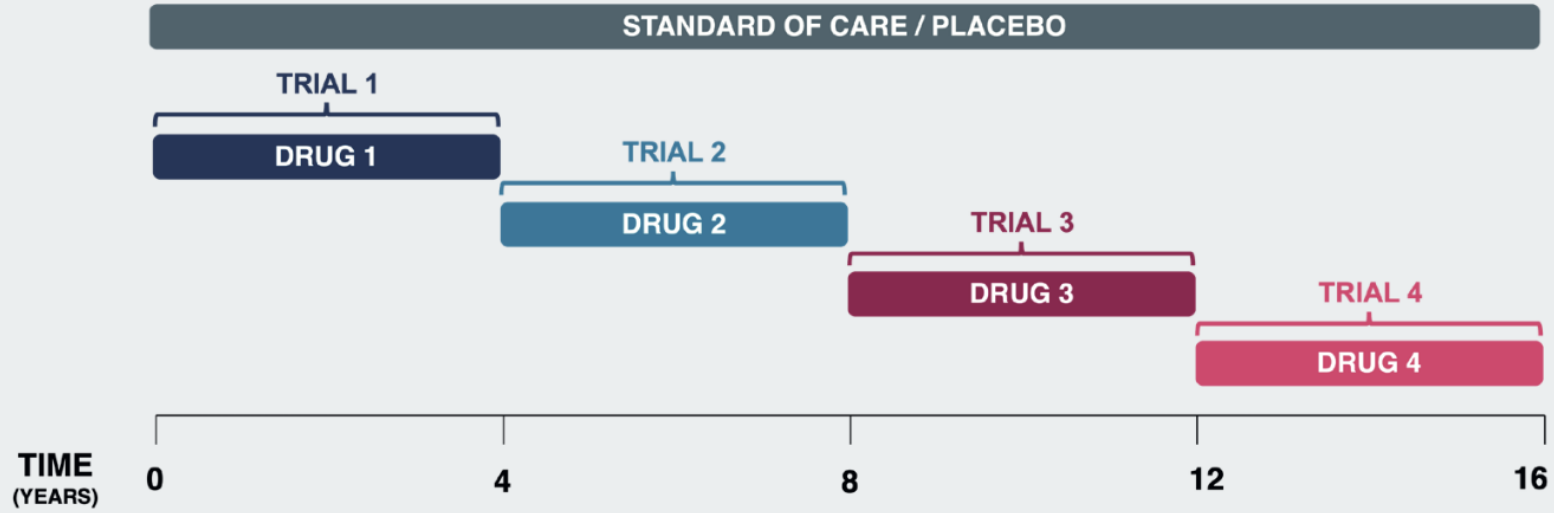
UKRI MRC Clinical Trials Unit | UCL | ECTU Edinburgh Clinical Trials Unit

Multi-Arm Multi-Stage (MAMS) adaptive Platform Trials

Conventional trial design

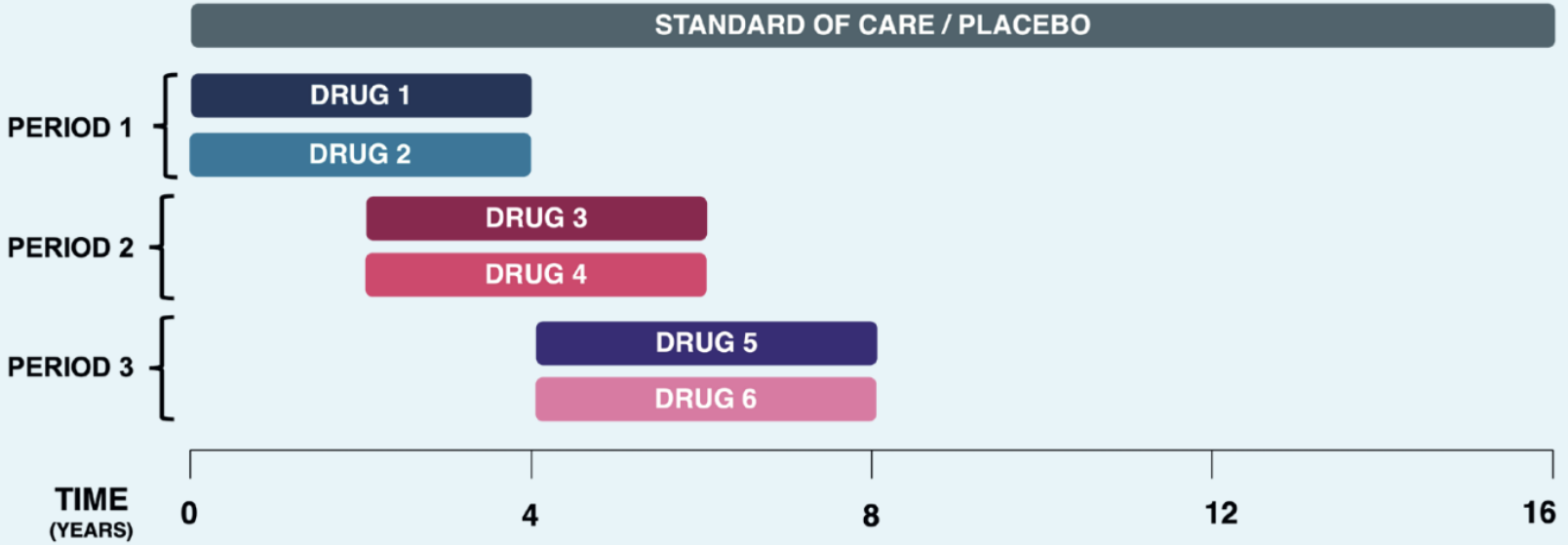
16 years required to complete trialing of 4 treatments



MND-SMART

<7 years required to complete trialing of 4 treatments

Additional drugs can be introduced driving efficiencies in time, cost and participant burden.



Team MND SMART

Inter-disciplinary team

pwMND

NDD scientists

Drug discovery expertise
Cancer / Pharma

Digital – Data scientists

Trial methodology

Trialists and neurologists

Funders / Charities / UK DRI

Innovation supporting decentralised trials

IMP couriered to participants homes

Video conferencing

E-consenting

Validation of remote outcome measures

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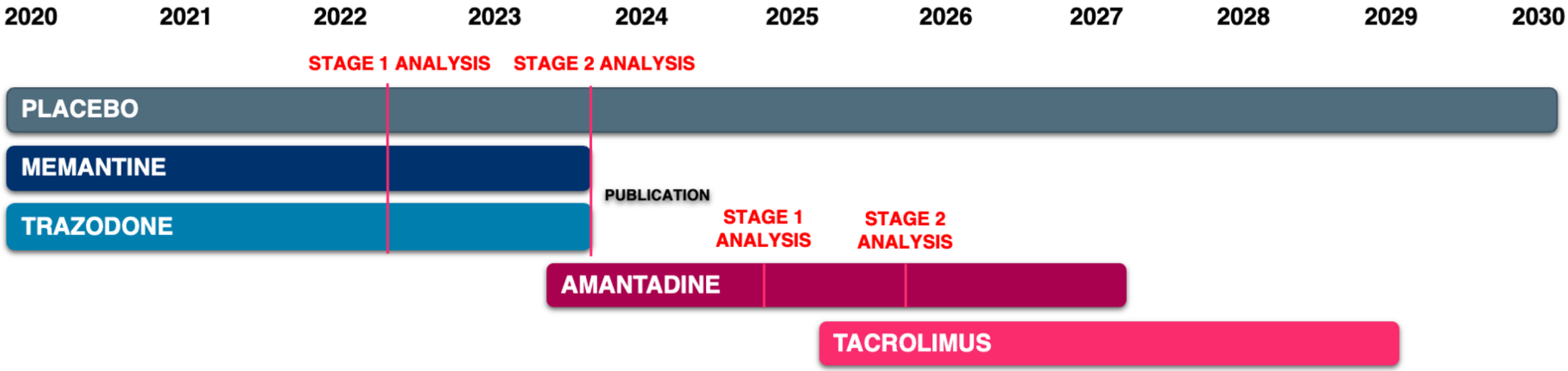
Pioneering design: A Platform for definitive Phase 3 MND trials

Seamless flexible, efficient, and dynamic staged analysis including blood-based biomarkers - A platform ready for Pharma

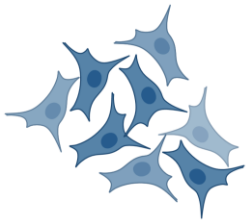


Primary outcome measures:
Participant functioning (ALS-FRS(R)) + survival

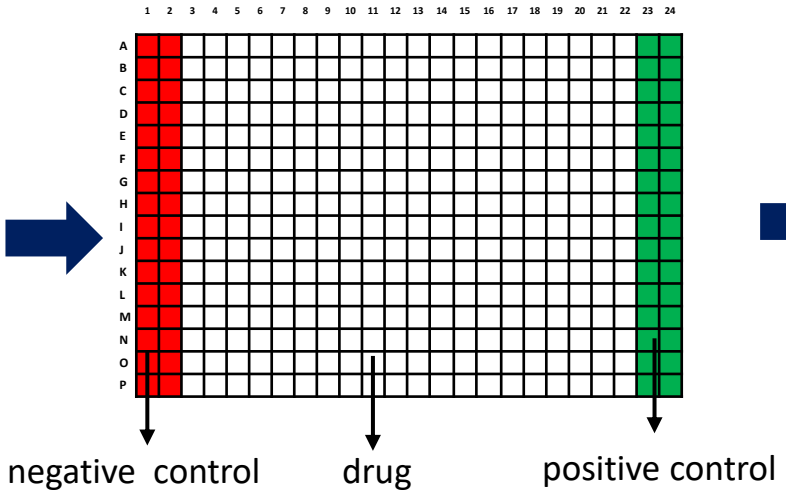
Secondary outcome measures:
Neurofilament light chain
Cognition (ECAS), mood (HADS), quality of life, safety

A new era in drug discovery

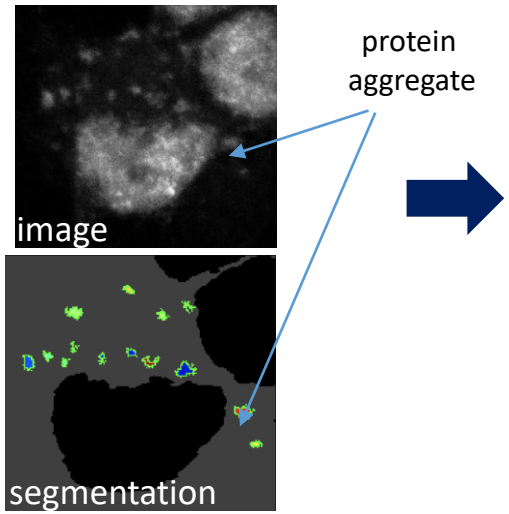
1. Cells are plated in 384 well plates for screening



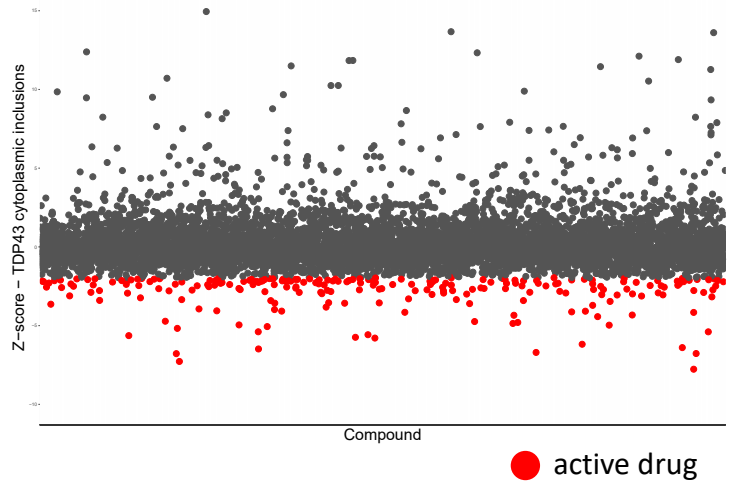
2. Drug treatment
6652 small molecules, 1 dose, 3 replicates



3. Automated image segmentation and analysis



4. 'Hit' identification



High throughput human stem cell-based model systems

- TDP43 aggregation
- Motor neuron excitotoxicity
- Astrocyte reactivity
- Astrocyte anti-oxidant
- Microglial inflammation

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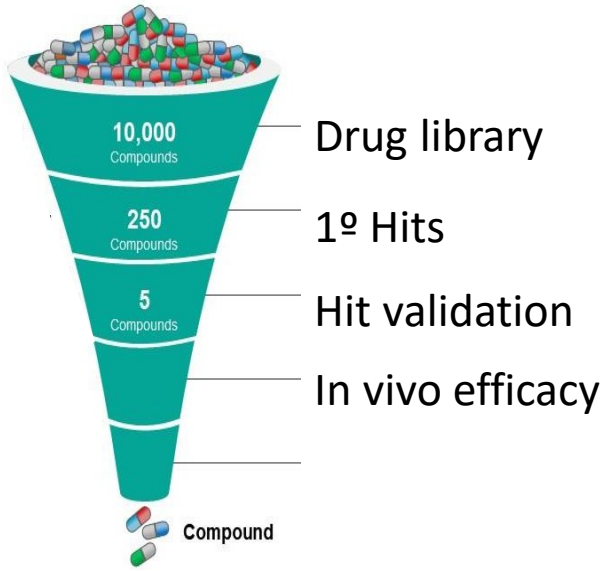
Multi-modal approach for drug selection

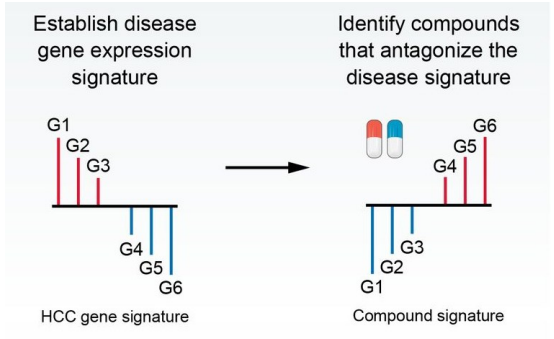


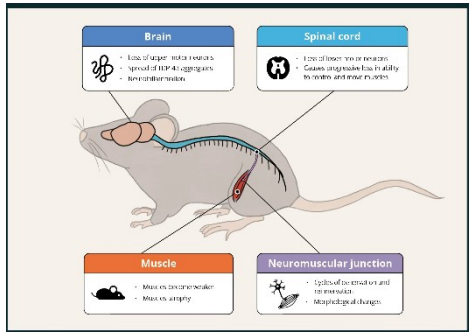
Drug library

1º Hits

Hit validation

In vivo efficacy





High throughput screening assays

AI/ML Computational drug screening

Systematic literature reviews

Animal models

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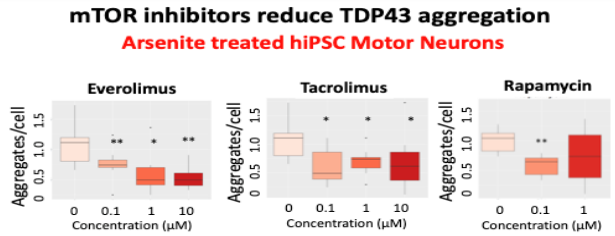
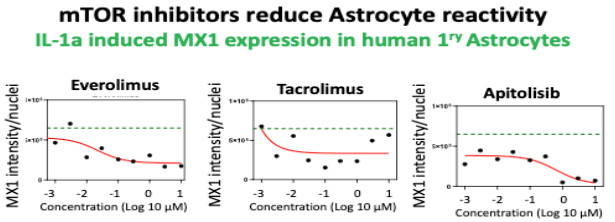
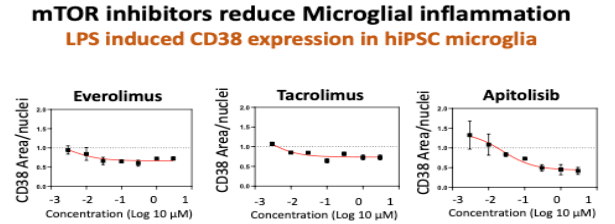
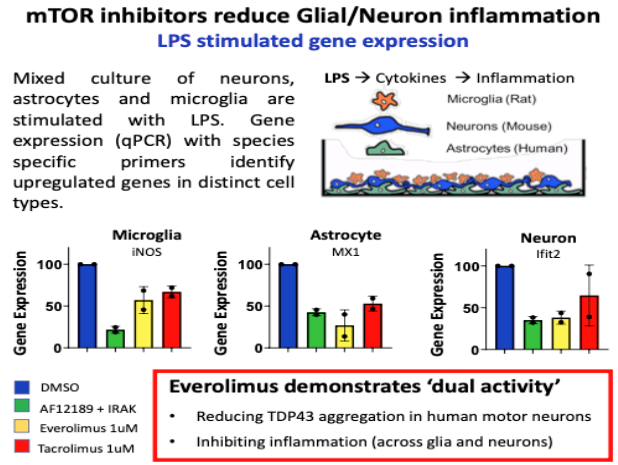
A new era in drug discovery

- **Tacrolimus** (calcineurin – mTOR inhibitor)
- Compelling data from human discovery platforms. Reduces:
  - TDP43 aggregation
  - Astrocyte reactivity
  - Microglial inflammation
  - Glial/neuron inflammation









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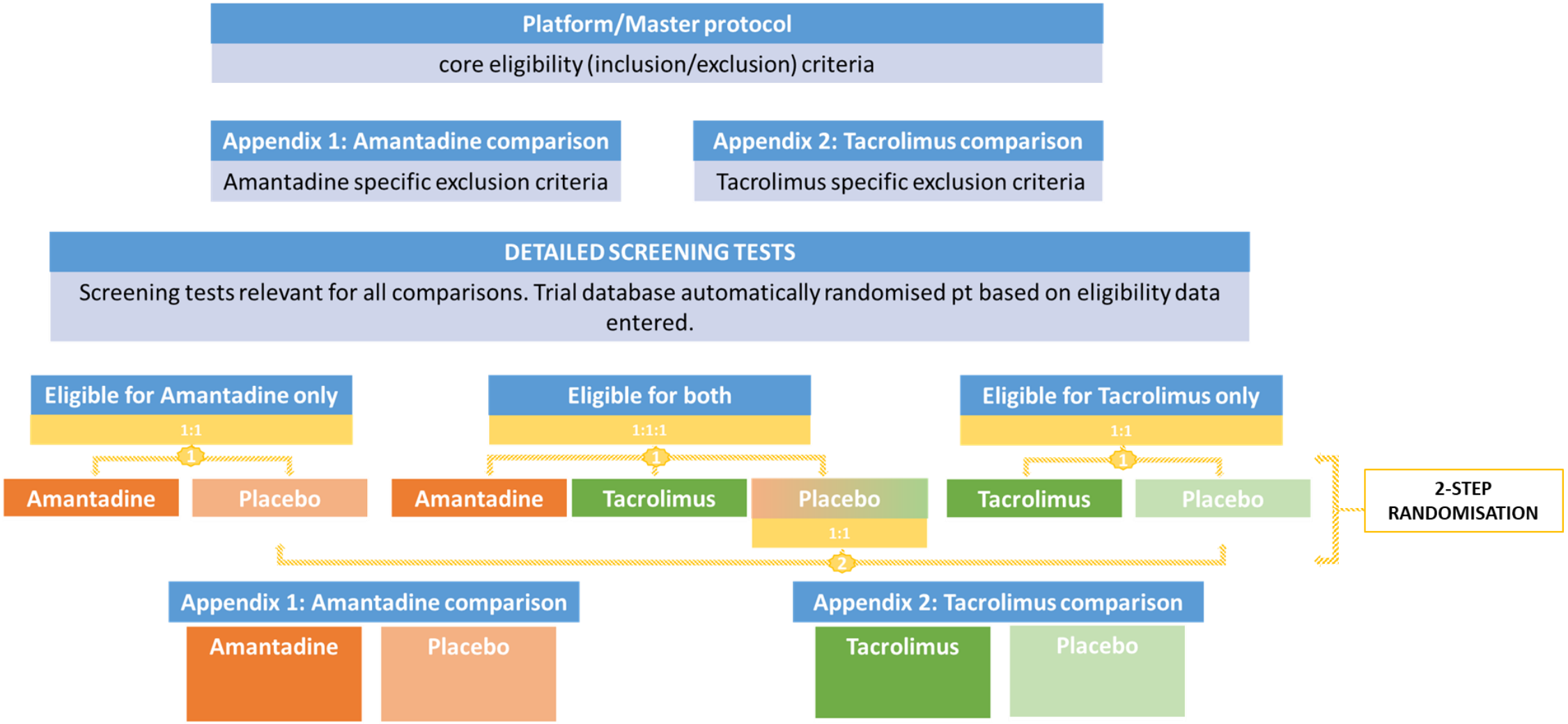
Pioneering design: A Platform for definitive Phase 3 MND trials

Protocol amendments accommodating: Different screening criteria, routes of administration, dosing schedules, safety monitoring

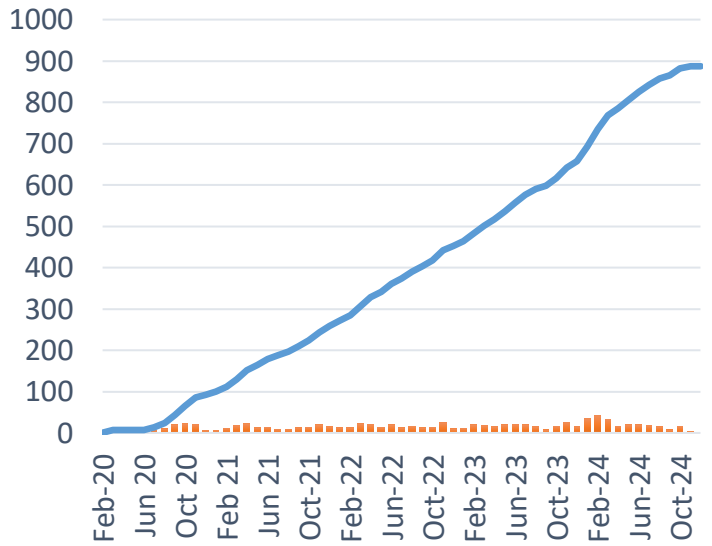


Delivering the largest ever trial for MND in the UK

Unprecedented speed and scale

Launch of the randomised trial amidst challenges of Covid-19	2020
Sites in the UK across **all 4 nations**	22
Randomised participants	>900
Years in operation	4
Interventions conclusively evaluated	2

1/2 **Time compared to conventional trial design**



Recruitment rate of c.15 participants/month

Delivering equity of access for pwMND across the UK

New sites opening 2025 in Leicester, York, Scarborough, Imperial, Liverpool, Hull

12 sites had no prior experience in delivering MND trials

Pioneering design: A Platform for definitive Phase 3 MND trials

Safety and efficacy of memantine and trazodone versus placebo for motor neuron disease (MND SMART): stage two interim analysis from the first cycle of a phase 3, multiarm, multistage, randomised, adaptive platform trial

*Suvankar Pal, Jeremy Chataway, Robert Swingler, Malcolm R Macleod, Neil O Carragher, Giles Hardingham, Bhuvaneish Thangaraj Selvaraj, Colin Smith, Charis Wong, Judith Newton, Dawn Lyle, Amy Stenson, Rachel S Dakin, Amarachi Ihenacho, Shuna Colville, Arpan R Mehta, Nigel Stallard, James R Carpenter, Richard A Parker, Catriona Keerie, Christopher J Weir, Bruce Virgo, Stevie Morris, Nicola Waters, Beverley Gray, Donald MacDonald, Evan MacDonald, Mahesh K B Parmar, Siddharthan Chandran, on behalf of the MND SMART Investigators**

www.thelancet.com/neurology **Published online September 19, 2024** **https://doi.org/10.1016/S1474-4422(24)00326-0**

- **Primary interim analysis population: 530 participants**
  - 175 (33%) memantine, 175 (33%) trazodone, 180 (34%) placebo
- **Characteristics similar across groups**
  - age, sex, years since first symptoms, years since diagnosis, ALSFRS-R score, MND subtype, and site of onset
- **Characteristics were typical for the wider MND population**
- **Withdrawals evenly distributed across treatment groups**

MND–SMART
Clinical trials for MND

The Edinburgh MND Clinical Trials Centre has randomised >175 participants

Clinical Research Nurse Specialists:

Judy Newton, Dawn Lyle,

Ethan Stoker, Isaac Chau

Clinical Research Fellows

Research Practitioners

Consultant Neurologists:

Suvankar Pal, Siddharthan Chandran,
Maria Stavrou

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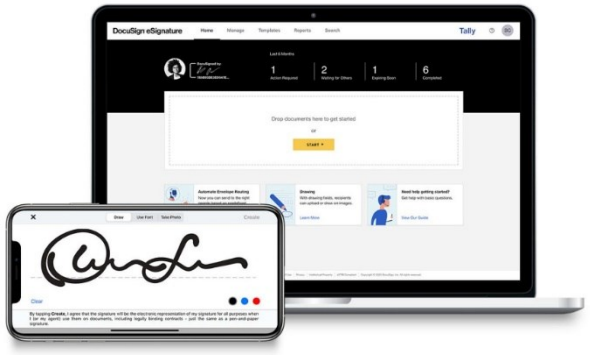
MND SMART co-production alongside people with MND

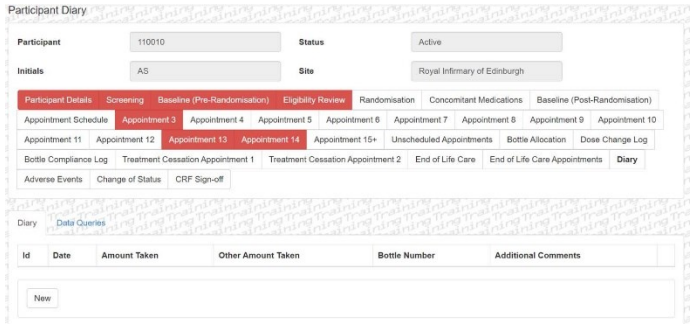
- Representation on Trial Steering Committee
- Study design
  - Drug selection
  - Routes of administration
  - Dosing schedules
  - Use of placebo
- Review of participant facing documentation
- Regulatory submissions
- Grant submissions
- Co-authorship of outputs

MND SMART co-production alongside people with MND

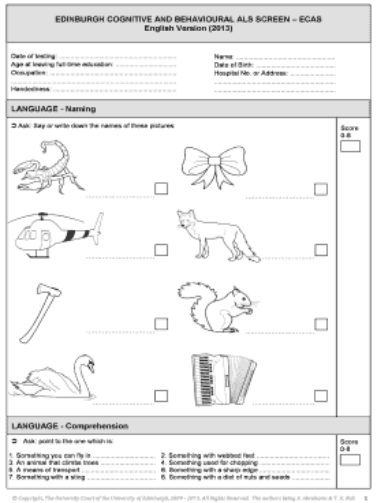


E-consenting

Video conference follow ups



Electronic diary cards



Remote ECAS

Continuous innovation supporting decentralisation

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Transforming the conversation for people with MND

"The trial is important in that I genuinely feel it to be a crucial component of my overall care package.

The opportunity to meet with the research team, together with the repeated completion of testing and blood sampling, gives me an up to date measure of my level of stability or indeed, the extent of any progression. It is also therapeutic in that I have a safe space where I can offload to someone not connected to me directly, i.e. family & friends.

For myself and my family it creates a sense of hope, a life jacket, that prevents us from emotionally drowning.

The solution to cracking the MND code will come and after experiencing, and feeling, the expertise of those working on finding those solutions, I am more confident than I have ever been that positive change is only over the horizon; we will see it soon."

Steve Barrett OBE, MND-SMART Participant

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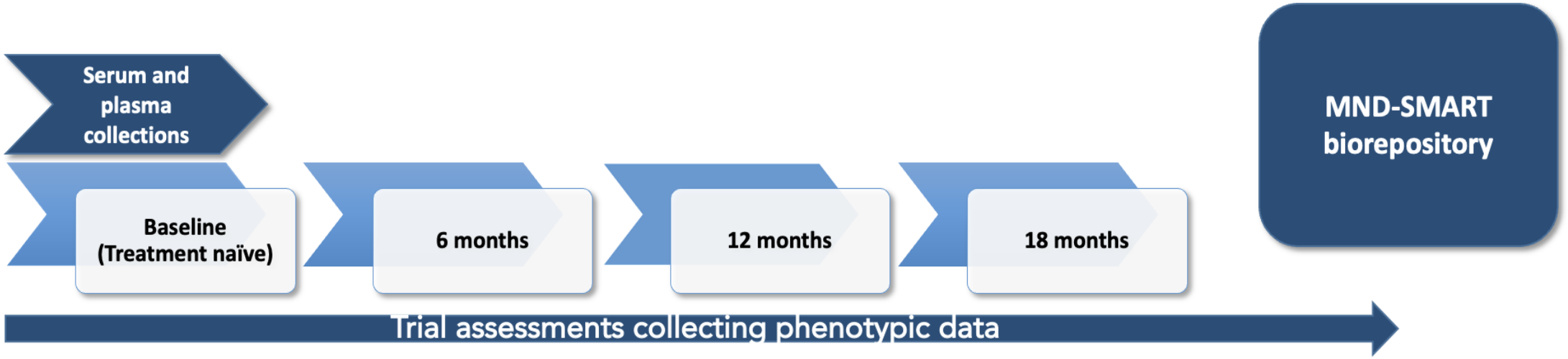
MND SMART – A platform for reverse translation



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UK Dementia Research Institute

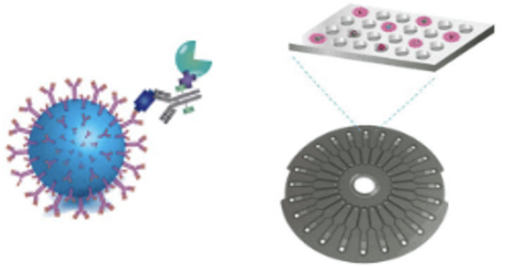
MND SMART – Fostering international collaboration

UK Dementia Research Institute

MRC Protein Phosphorylation and Ubiquitylation Unit

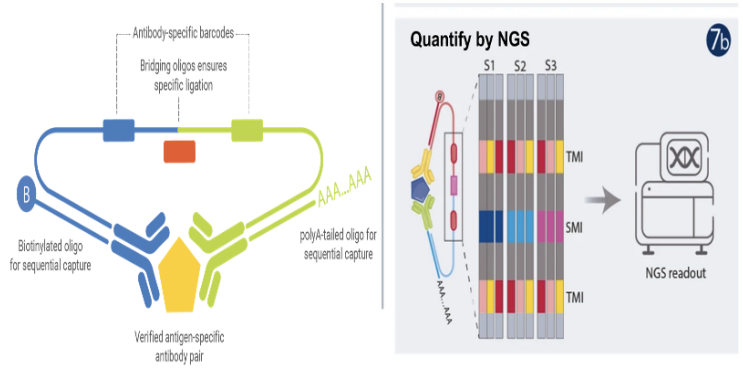
Gates Ventures

Single Molecular Array (SIMOA)



Simoa® Technology | Quanterix

NUcleic acid Linked Immuno-Sandwich Assay (NULISA™)



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UK Dementia Research Institute

Development and validation of speech biomarkers

Providing **health insights** to people living with **neurodegenerative diseases including MND**

through language agnostic analysis of speech

Captured remotely through a user-friendly and intuitive app, available on any mobile phone

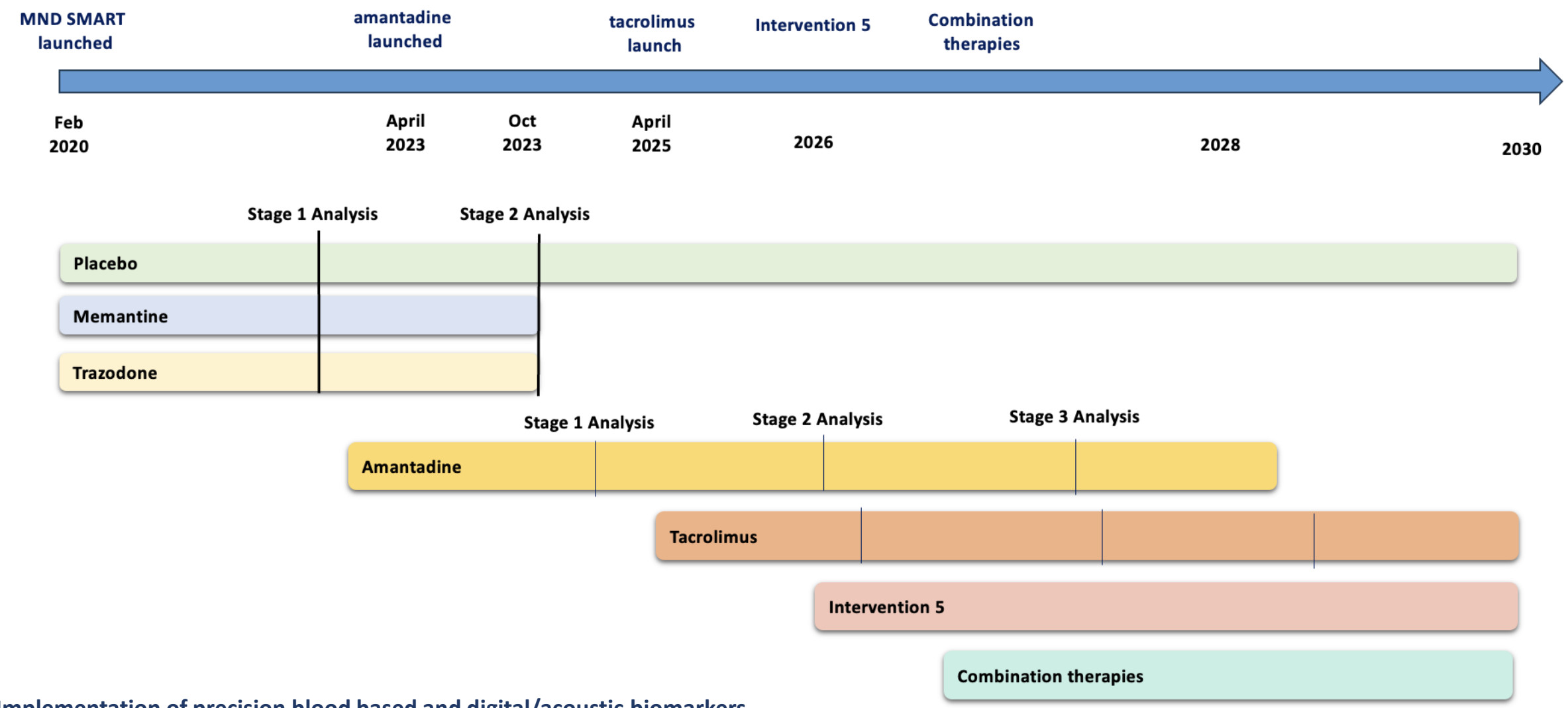
Delivering a globally relevant and scalable solution that democratises health technology

Investigate advances in **speech processing and AI** transforming diagnosis and monitoring

Acoustic signals that detail **"how we speak"** rather than "what we say", bypassing language barriers

Combine leading **speech technology and clinical expertise** to create a global solution

Forward momentum



Implementation of precision blood based and digital/acoustic biomarkers

Embedding experimental medicine approaches

Acknowledgements

Trial Management group

Siddharthan Chandran, Director UK Dementia Research Institute
Suvankar Pal, Professor of Neurodegenerative Disorders & Clinical Trials
Chris Weir, Professor of Medical Statistics and Clinical Trials
Judy Newton, MND National Lead Consultant Nurse
Amy Stenson, MND SMART Trial manager
Robert Swingler, Consultant Neurologist, London
Jeremy Chataway, Professor of Neurology, University College London

Trial Committees

Trial steering committee - Helen Ford (Chair)
Independent Data Monitoring Committee -Steve Wroe (Chair)

Trial Sponsors

ACCORD – NHS Lothian and University of Edinburgh

Funders:

Euan MacDonald Centre
MND Scotland
My Name'5 Doddie Foundation
MND Association
Alan Davidson Foundation
Baillie Gifford
LifeArc

Key Collaborators

Mahesh Parmar, Professor of Medical Statistics and Epidemiology, Director of MRC Clinical Trials Unit at UCL
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Neil Carragher, Chair of Drug Discovery and Director of Science Edinburgh Cancer Research
Henrik Zetterburg, UK Dementia Research Institute Biomarker Factory, UCL
Gilies Hardingham, Director, UK Dementia Research Institute at Edinburgh
Nigel Stallard, Professor of Medical Statistics, University of Warwick
Malcolm Macleod, Professor of Neurology and Translational Neuroscience, University of Edinburgh
Bhuvaneish Selvaraj, UK Dementia Research Institute at Edinburgh

PPIE Group

Bruce Virgo, Steven Barrett, Jacqueline Casey, Nicola Waters, Steven Morris

Site teams

Edinburgh - Suvankar Pal
Dundee - Ian Morrison
Glasgow – George Gorrie
Salford – Hisham Hamdalla
Aberdeen – Callum Duncan
Craigavon - Raeburn Forbes
Inverness – Javier Carod Artal
Exeter – Tim Harrower
St George's – Pablo Garcia-Reitboeck
W Suffolk – Francesca Crawley
Birmingham – Venkat Srinivasan
Ipswich – Clare Galton
Newcastle – Tim Williams
Cardiff – Ken Dawson
Royal London – Aleks Radunovic
Southampton – Ashwin Pinto
Cambridge – Rhys Roberts
Norfolk – Godwin Mamutse
Poole – Charles Hillier
Sheffield – Chris McDermott
Kings – Ammar Al-Chalabi
Brighton – Andrew Barritt
York – Malcolm Proudfoot